



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children (Last updated April 14, 2020; last reviewed April 14, 2020)

Many antiretroviral (ARV) agents and combinations are available; some are not recommended for use as part of an initial regimen in ARV-naive children, although they may be used in ARV-experienced children. This section describes ARV drugs and drug combinations that either are not recommended for use in ARV-naive children or that lack sufficient data to recommend their use in ARV-naive children. Several ARV drugs that are no longer available or that have not been recommended for use in children for several years have been removed from this chapter, including the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and didanosine; the protease inhibitors (PIs) indinavir, nelfinavir, saquinavir, tipranavir (TPV), and fosamprenavir; and **the fusion inhibitor** enfuvirtide. Information about these agents is available in [Archived Drugs](#).

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) classifies ARV drugs and drug combinations that are not recommended for use in ARV-naive children into one of three categories:

- **Not Recommended for Initial Therapy:** These include ARV drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because they produce an inferior virologic response, they pose potential serious safety concerns (including potentially overlapping toxicities), they are associated with pharmacologic antagonism, or there are better options within a drug class. These drugs and drug combinations are listed in Table 9, **and selected drugs or drug combinations are discussed below**.
- **Insufficient Data to Recommend for Initial Therapy:** ARV drugs and drug combinations that are approved for use in adults but that have insufficient, limited, and/or no pharmacokinetic (PK) or safety data for children cannot be recommended for initial therapy in children. However, these drugs and drug combinations may be appropriate to consider when managing treatment-experienced children (see [Management of Children Receiving Antiretroviral Therapy](#)). These drugs are also listed in Table 9, **and selected drugs or drug combinations are discussed below**.
- **Antiretroviral Drug Regimens That Are *Never* Recommended:** Several ARV drug and drug combinations should never be used in children or adults. These are summarized in Table 10. Clinicians should also be aware of the components of fixed-dose combination (FDC) tablets so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Antiretroviral Drugs and Drug Combinations Not Recommended for Initial Therapy in Children

Atazanavir without Ritonavir or Cobicistat Boosting

Although unboosted atazanavir (ATV) is approved by the Food and Drug Administration (FDA) for use in treatment-naive adolescents aged ≥ 13 years and weighing ≥ 40 kg who are unable to tolerate ritonavir (RTV), data from the IMPAACT/PACTG 1020A study indicate that adolescents require higher doses of unboosted ATV (as measured by mg/m² of body surface area) than adults in order to achieve adequate drug concentrations.¹ The Panel **does not recommend** using ATV without RTV boosting because of these findings.

Regimens that Contain Only Nucleoside Reverse Transcriptase Inhibitors

In adult trials, regimens that contain only NRTIs have shown less potent virologic activity than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based or PI-based regimens.^{2,3} Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited to small observational studies.^{4,5} In a study on the use of the triple-NRTI regimen abacavir plus lamivudine (3TC) plus zidovudine in ARV-experienced children, this combination showed evidence of only modest viral suppression; only 10 of the 102

children had viral loads of <400 copies/mL at Week 48 of treatment.⁶ Therefore, regimens that contain only NRTIs **are not recommended** for treatment-naïve or treatment-experienced children.

Regimens that Contain Three Drug Classes

The Panel **does not recommend** using regimens that contain agents from three drug classes as initial regimens (e.g., an NRTI plus an NNRTI plus a PI or an integrase strand transfer inhibitor plus an NRTI plus a PI or NNRTI). Although studies of regimens that contain three classes of drugs have demonstrated that these regimens are safe and effective in ARV-experienced children and adolescents, these regimens have not been studied as initial regimens in treatment-naïve children and adolescents. These regimens also have the potential to induce resistance to three drug classes, which could severely limit future treatment options.⁷⁻¹¹ Ongoing studies are investigating the use of drugs from three drug classes to treat neonates.

Regimens that Contain Three Nucleoside Reverse Transcriptase Inhibitors and a Non-Nucleoside Reverse Transcriptase Inhibitor

Data are currently insufficient to recommend using a regimen that contains three NRTIs plus an NNRTI in young infants. A review of nine cohorts from 13 European countries suggested that this four-drug regimen produced responses that were superior to the responses observed in patients receiving boosted-PI regimens or three-drug NRTI regimens.¹² There has been speculation that poor tolerance and poor adherence to a PI-based regimen may account for some of the differences. The ARROW trial, conducted in Uganda and Zimbabwe, randomized 1,206 children (with a median age of 6 years) to receive either a standard NNRTI-based, three-drug regimen (**two NRTIs and one NNRTI**) or a four-drug regimen (three NRTIs and one NNRTI). After a 36-week induction period, the children on the four-drug regimen continued treatment on a regimen that contained **two** NRTIs plus **one** NNRTI or a three-NRTI regimen. Although improvements in CD4 T lymphocyte (CD4) cell counts were observed **at Week 36 (with a percentage change of approximately 14.4% in the four-drug arm compared to 12.6% in the three-drug arm)**, these benefits were not sustained after patients switched to the three-drug regimens **for the duration of the study. Furthermore, no differences in viral load suppression rates were observed between the two arms at Week 36.**¹³ Because three-drug regimens have been shown to be effective and well tolerated, and because efficacy data is lacking for the four-drug regimen, the Panel **does not currently recommend** the four-drug regimen.

Antiretroviral Drugs and Combinations with Insufficient Data to Recommend for Initial Therapy in Children

Several ARV drugs and drug regimens are not recommended for use as initial therapy in ARV-naïve children or for specific age groups because of insufficient pediatric data. In some cases, new agents have shown promise in adult clinical trials but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. In addition, some dosing schedules may not be recommended in certain age groups due to insufficient data. As new data become available, these agents may become recommended agents or regimens. These agents and regimens are summarized below and are also listed in Table 9.

Doravirine-Based Regimens

Doravirine (DOR) is an NNRTI that is available as both a single-drug tablet and an FDC tablet that contains DOR 100 mg/3TC 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg and is marketed as Delstrigo. Efficacy studies in adults have demonstrated that DOR/3TC/TDF is noninferior to efavirenz (EFV)-based regimens and darunavir (DRV)-based regimens. DOR compared favorably to the other drugs in these trials in terms of adverse events. Currently, DOR is not approved for use in children or adolescents aged <18 years, but there are ongoing studies of DOR in children and adolescents. At this time, the Panel **does not recommend** the use of DOR in children or adolescents.

Darunavir with Low-Dose Ritonavir-Based Regimens Administered Once Daily for Children Aged ≥ 3 Years to < 12 Years

While modeling studies identified a once-daily dosing schedule for darunavir/ritonavir (DRV/r) that is now approved by the FDA, the Panel is concerned about the lack of direct PK studies for this approach in individuals aged ≥ 3 years to < 12 years. Therefore, there is insufficient data to recommend once-daily dosing for initial therapy in this age group. For children aged ≥ 3 years to < 12 years, twice-daily DRV/r is a *Preferred* drug combination. For older children who have undetectable viral loads while receiving a twice-daily DRV/r-based regimen, practitioners can consider switching to once-daily DRV/r dosing if no DRV-associated resistance mutations are present. Once-daily dosing helps support adherence by making this drug combination easier to use.

Efavirenz-Based Regimens for Children Aged ≥ 3 Months to 3 Years

EFV is approved by the FDA for use in children aged > 3 months and weighing ≥ 3.5 kg. An EFV-based regimen has been shown to have variable PKs in studies of the very young; because of this, the Panel does not recommend using EFV in children aged < 3 years at this time (see the [Efavirenz](#) section in [Appendix A: Pediatric Antiretroviral Drug Information](#)). When use of EFV is being considered for children aged < 3 years, cytochrome P450 (CYP) 2B6 genotyping should be performed, if available, in order to predict a patient's metabolic rate for EFV. Therapeutic drug monitoring can also be considered.

Etravirine-Based Regimens

Etravirine (ETR) is an NNRTI that has been studied in treatment-experienced children aged ≥ 1 years and is now approved by the FDA for use in children aged ≥ 2 years and weighing ≥ 10 kg.¹⁴⁻¹⁶ It is associated with multiple interactions with other ARV drugs, including TPV/ritonavir, ATV/ritonavir, and unboosted PIs, and must be administered twice daily. It is unlikely that the use of ETR will be studied in treatment-naïve children.

Maraviroc-Based Regimens

Maraviroc (MVC) is an entry inhibitor that is approved by the FDA for use in children aged ≥ 2 years and weighing ≥ 10 kg who have CCR5-tropic HIV-1. It has been used infrequently in children. A recent dose-finding study administered both the liquid and tablet formulations of MVC to treatment-experienced children aged 2 to 18 years who were divided into four age cohorts.¹⁷ The initial dose was based on body surface area and scaled from the recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP3A4 inhibitor or inducer.¹⁸ MVC has multiple drug interactions and must be administered twice daily. In addition, tropism assays must be performed prior to use to ensure the presence of only CCR5-tropic virus.

Table 9. Antiretroviral Regimens or Components That Are Not Recommended for Initial Treatment of HIV Infection in Children

ARV Regimen or Component	Rationale
Unboosted ATV-containing regimens in children	Reduced exposure
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Potential to induce multiclass resistance Use as an initial regimen in children has not been studied
Regimens containing three NRTIs and one NNRTI	Added cost and complexity outweighs any benefit
Full-dose RTV or use of RTV as the sole PI	GI intolerance Metabolic toxicity
LPV/r dosed once daily	Reduced drug exposure
DOR-based regimens	Insufficient data to recommend
Once-daily DRV-based regimens in children aged ≥ 3 years to < 12 years	Insufficient data to recommend
EFV-based regimens for children aged < 3 years	Appropriate dose not determined
ETR-based regimens	Insufficient data to recommend
MVC-based regimens	Insufficient data to recommend
Unboosted DRV	Use without RTV has not been studied
Full-dose, dual-PI regimens	Insufficient data to recommend Potential for added toxicities
TDF-containing regimens in children aged < 2 years	Potential bone toxicity Appropriate dose has yet to be determined

Key: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DOR = doravirine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; GI = gastrointestinal; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Table 10. Antiretroviral Regimens or Components That Are Never Recommended for Treating HIV in Children

ARV Regimens That Are <u>Never</u> Recommended for Use in Children		
Regimen	Rationale	Exceptions
One ARV Drug Alone (Monotherapy)	Rapid development of resistance Inferior antiviral activity compared to regimens that include ≥ 3 ARV drugs Monotherapy “holding” regimens are associated with more rapid CD4 count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4–6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	Rapid development of resistance Inferior antiviral activity compared to regimens that include ≥ 3 ARV drugs	Not recommended for initial therapy Some clinicians may opt to continue using two NRTIs alone in patients who achieve virologic goals with this regimen.
TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen	High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naïve adults	No exceptions
ARV Components That Are <u>Never</u> Recommended for Use as Part of an ARV Regimen for Children		
Regimen	Rationale	Exceptions
Dual-NNRTI Combinations	Enhanced toxicity	No exceptions
Dual-NRTI Combination of 3TC plus FTC	Similar resistance profile and no additive benefit	No exceptions
NVP as Initial Therapy in Adolescent Girls with CD4 Counts >250 cells/mm³ or Adolescent Boys with CD4 Counts >400 cells/mm³	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	Only if benefit clearly outweighs risk

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21610486>.
2. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS*. 2003;17(14):2045-2052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14502007>.
3. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. 2003;17(7):987-999. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12700448>.
4. Saavedra J, McCoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Interscience Conference on Antimicrobial Agents and Chemotherapy. 2001. Chicago, Illinois.
5. Handforth J, Sharland M. Triple nucleoside reverse transcriptase inhibitor therapy in children. *Paediatr Drugs*. 2004;6(3):147-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15170362>.
6. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency

virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. 2001;107(1):E4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11134468>.

7. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769-1773. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069252>.
8. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-1881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10601506>.
9. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(7):659-663. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12237599>.
10. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial—PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113-1121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10954886>.
11. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
12. Judd A, and EP, Paediatric HIV Cohort Collaboration study group in EuroCoord. Early antiretroviral therapy in HIV-1-infected infants, 1996–2008: treatment response and duration of first-line regimens. *AIDS*. 2011;25(18):2279-2287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21971357>.
13. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23473847>.
14. Konigs C, Feiterna-Sperling C, Esposito S, et al. Pharmacokinetics and short-term safety and tolerability of etravirine in treatment-experienced HIV-1-infected children and adolescents. *AIDS*. 2012;26(4):447-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22156961>.
15. Tudor-Williams G, Cahn P, Chokephaibulkit K, et al. Etravirine in treatment-experienced, HIV-1-infected children and adolescents: 48-week safety, efficacy and resistance analysis of the Phase II PIANO study. *HIV Med*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24589294>.
16. MacBrayne CE, Rutstein R, Yogev R, et al. Etravirine pharmacokinetics in treatment-experienced children ages 1- <6 years. Abstract 465. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/etravirine-pharmacokinetics-treatment-experienced-children-ages-1->
17. Giaquinto C, Mawela MP, Chokephaibulkit K, et al. Pharmacokinetics, Safety and efficacy of maraviroc in treatment-experienced pediatric patients infected with CCR5-Tropic HIV-1. *Pediatr Infect Dis J*. 2018;37(5):459-465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29023357>.
18. Vourvahis M. Update from Study A4001031: maraviroc pharmacokinetics in CCR5-tropic HIV-1-infected children aged 2 to < 18 years. IAS Conference on HIV Pathogenesis, Treatment and Prevention. 2013. Kuala Lumpur, Malaysia. Available at: <http://www.abstract-archive.org/Abstract/Share/13916>.